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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/530,747	10/23/2000	Christoph Kessler	4817/OR	5088

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PATENT LAW DEPARTMENT
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EXAMINER	
TAYLOR, JANELL E	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/530,747	KESSLER ET AL.	
	Examiner	Art Unit	
	Janell Taylor Cleveland	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The following is a FINAL REJECTION. A Response to Arguments section follows the Office Action.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-2, 4-5, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livak et al (USPN 5,538,848) in view of Western et al. (5,882,857).

The claims are drawn to a method for the detection of a nucleic acid comprising the steps: (a) producing a plurality of amplificates of a section of the nucleic acid with the aid of two primers, one of which can bind to a first binding sequence (A) of one strand of the nucleic acid and the other can bind to a second binding sequence (C') which is essentially complementary to a sequence C which is located in the 3' direction from A and does not overlap A, in the presence of a probe with a binding sequence D which can bind to the third sequence (B) located between the sequences A and C or to the complement (B') thereof, wherein this probe contains a reporter group and a quencher group, using a polymerase having 5' nuclease activity, and (b) detecting the nucleic acid by measuring a signal which is caused by the release of the reporter group, wherein the amplificates formed with the aid of the primers have a length of less than 75 nucleotides. Other claims are drawn to the probe sequence not overlapping that of the

primers, the binding sequences not being specific for the nucleic acid to be detected, the primer being less than 61 nucleotides in length, the probe being labeled with a fluorescent quencher as well as a fluorescent dye, and to the nucleotides being complementary to A, G, C, and T.

Livak et al. teach "A method is provided for monitoring the progress of nucleic acid amplifications that rely on a nucleic acid polymerase having 5' to 3' exonuclease activity [such as Taq polymerase, which also has 5' nuclease activity, as disclosed in the claims]. An important feature of the method is providing an oligonucleotide probe having a *reporter molecule and a quencher molecule* at either end such that the quencher molecule substantially quenches any fluorescence from the reporter whenever the oligonucleotide probe is in a single stranded state and such that the reporter is substantially unquenched whenever the oligonucleotide probe is in a double stranded state hybridized to a target polynucleotide." (Abstract). Livak et al. also teach "The binding site of the oligonucleotide probe is located between the PCR primers used to amplify the target polynucleotide." (Col. 4, line 20). In other words, Livak et al. teach two primers and a probe which hybridizes in between the primers, and contains a reporter and a quencher molecule.

Livak does not teach that the amplificate is less than 75, or 61, nucleotides in length.

Western et al. teaches "target sequence of a target polynucleotide--a sequence of nucleotides to be identified, *usually existing within a portion (target polynucleotide) or all of a polynucleotide analyte*, the identity of which is known to an extent sufficient to

allow preparation of various primers and other molecules necessary for conducting an amplifcation of the target sequence contained within the target polynucleotide. In general, in primer extension amplification primers hybridize to, and are extended along (chain extended), at least the target sequence within the target polynucleotide and, thus, the target sequence acts as a template. The extended primers are chain "extension products'. The target sequence usually lies between two defined sequences but need not. In general, the primers and other *probe polynucleotides* hybridize with the defined sequences or with at least a portion of such target polynucleotide, usually at least a ten nucleotide segment at the 3' end thereof and preferably at least 15, frequently 20 to 50 nucleotide segment thereof. *The target sequence usually contains from about 30 to 5000 or more nucleotides, preferably 50 to 1000 nucleotides. The target polynucleotide is generally a fraction of a larger molecule or it may be substantially the entire molecule (polynucleotide analyte).*" (Col. 12 bridging Col. 13). Therefore, Western et al teach an amplification product of 30 to 5000 nucleotides, which is capable of hybridizing with a probe.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Livak with those of Western. This is because it would have been obvious to use amplificates of less than 75 nucleotides to hybridize the probe to, as Western taught that probes were capable of hybridizing to amplficates from a wide variety of lengths. Furthermore, it would have been obvious to one of ordinary skill in the art that as long as the amplificate was long enough to be able to hybridize with the full length of the probe, the size of the amplificate would have been

irrelevant. Although Western does not teach that the probe is comprised of a reporter/quencher system, it would have been obvious to one of ordinary skill in the art at the time of the invention that the reporter/quencher system would have been useful with the probe of Western et al. for identifying the target nucleic acid.

3. Claims 3 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livak et al. in view of Western.

The claims are drawn to a method for the detection of a nucleic acid comprising the steps: (a) producing a plurality of amplificates of a section of the nucleic acid with the aid of two primers, one of which can bind to a first binding sequence (A) of one strand of the nucleic acid and the other can bind to a second binding sequence (C') which is essentially complementary to a sequence C which is located in the 3' direction from A and does not overlap A, in the presence of a probe with a binding sequence D which can bind to the third sequence (B) located between the sequences A and C or to the complement (B') thereof, wherein this probe contains a reporter group and a quencher group, using a polymerase having 5' nuclease activity, and (b) detecting the nucleic acid by measuring a signal which is caused by the release of the reporter group, wherein the amplificates formed with the aid of the primers have a length of less than 75 nucleotides. Other claims are drawn to the probe sequence not overlapping that of the primers, the binding sequences not being specific for the nucleic acid to be detected, the primer being less than 61 nucleotides in length, the probe being labeled with a fluorescent quencher as well as a fluorescent dye, and to the nucleotides being complementary to A, G, C, and T.

Livak et al. teach "A method is provided for monitoring the progress of nucleic acid amplifications that rely on a nucleic acid polymerase having 5' to 3' exonuclease activity [such as Taq polymerase, which also has 5' nuclease activity, as disclosed in the claims]. An important feature of the method is providing an oligonucleotide probe having a *reporter molecule and a quencher molecule* at either end such that the quencher molecule substantially quenches any fluorescence from the reporter whenever the oligonucleotide probe is in a single stranded state and such that the reporter is substantially unquenched whenever the oligonucleotide probe is in a double stranded state hybridized to a target polynucleotide." (Abstract). Livak et al. also teach "The binding site of the oligonucleotide probe is located between the PCR primers used to amplify the target polynucleotide." (Col. 4, line 20). In other words, Livak et al. teach two primers and a probe which hybridizes in between the primers, and contains a reporter and a quencher molecule.

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thus, the target sequence acts as a template. The extended primers are chain "extension products'. The target sequence usually lies between two defined sequences but need not. In general, the primers and other *probe polynucleotides* hybridize with the defined sequences or with at least a portion of such target polynucleotide, usually at least a ten nucleotide segment at the 3' end thereof and preferably at least 15, frequently 20 to 50 nucleotide segment thereof. *The target sequence usually contains from about 30 to 5000 or more nucleotides, preferably 50 to 1000 nucleotides. The target polynucleotide is generally a fraction of a larger molecule or it may be substantially the entire molecule (polynucleotide analyte).*" (Col. 12 bridging Col. 13). Therefore, Western et al teach an amplification product of 30 to 5000 nucleotides, which is capable of hybridizing with a probe.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Livak with those of Western. This is because it would have been obvious to use amplificates of less than 75 nucleotides to hybridize the probe to, as Western taught that probes were capable of hybridizing to amplficates from a wide variety of lengths. Furthermore, it would have been obvious to one of ordinary skill in the art that as long as the amplificate was long enough to be able to hybridize with the full length of the probe, the size of the amplificate would have been irrelevant. Although Western does not teach that the probe is comprised of a reporter/quencher system, it would have been obvious to one of ordinary skill in the art at the time of the invention that the reporter/quencher system would have been useful with the probe of Western et al. for identifying the target nucleic acid.

Neither Livak nor Western et al. teach the that the primer or probe is not specific for the target.

It would have been obvious to one of ordinary skill in the art to have a primer or probe which was known to amplify, or hybridize with, more than just the target nucleic acid. This is because it would have allowed the practitioner to amplify or detect multiple species of a genus, for instance, or to detect or amplify a sequence where the entire sequence was not known. This would have allowed for amplification and detection of a nucleic acid without the need to first sequence the nucleic acid.

Summary

Claims 1-9 are rejected under 35 U.S.C. 103(a). No claims are free of the prior art.

Response to Arguments

4. Applicant's arguments filed January 7, 2002 have been fully considered but they are not persuasive. In particular, Applicant has argued that Neither Livak nor Western teaches or suggests each and every element of the methods of claims 1-9. In particular, Applicant states that "the PTO fails to explain how Western teaches or suggests that a probe containing a reporter group can be degraded by a polymerase while bound to an amplificate having a length less than 75 nucleotides." The Western reference was used, however, to show that amplificates less than 75 nucleotides in length are capable of hybridizing probes. Applicant also states that "the PTO has failed to indicate why one of ordinary skill in the art would have any reasonable expectation that the use of a probe comprising a reporter group would have any expectation of

success in a method for the detection of a nucleic acid using amplificates less than 75 nucleotides in length. As acknowledged by the PTO, conventional detection methods using probes comprising reporter groups, such as the method of Livak, are limited to the use of much larger amplificates, typically of 150 nucleotides or more." First of all, the Examiner made no such admission about the "typical size" of amplificates, and specifically no reference was made to the amplificates being 150 nucleotides or more. Also, Applicant has made no showing of a reference to indicate the "typical" size of an amplificate, and therefore this is considered speculation and is not considered relevant. Furthermore, Applicant has argued that the amplificate should not only hybridize with the probe, as taught by Western, but should have an appropriate size and form to permit proper polymerase binding and extension to efficiently degrade the probe and release the reporter group. However, it is well established in the art that polymerases are capable of binding to, and extending, nucleic acids which are smaller in length than the claimed 75 bases. Absent a specific teaching to the contrary, one of ordinary skill in the art would have been motivated to use an amplificate less than 75 nucleotides in length with the method of Livak.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor Cleveland, whose telephone number is (703) 305-0273.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Any inquiries of a general nature relating to this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 305-3014 or 305-4227. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor Cleveland

February 12, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600